REMARKS/ARGUMENTS

I. Status of the Claims

Claims 8, 10, 19, 22 and 33 are pending.

Upon entry of the present amendment, claim 10 is canceled. New claim 33 is added with this amendment. Support for claim 33 is found, for example, at page 41, line 36 to page 42, line 23.

Both claims 8 and 19 are amended to delete the language "An antisense polynucleotide or," "a polypeptide selected from the group consisting of:" and parts (b) and (c).

Both claims 8 are 19 are amended to recite "wherein the sense strand thereof consists of a ribonucleotide sequence corresponding to the nucleotide sequence of SEQ ID NO: 13." Support for this amendment is found in original claim 10 and throughout the specification. No new matter is introduced.

II. Priority

This application claims the benefit of the filing date of Application No. 60/414,867 as allowed under 35 U.S.C. 119(e) or 35 U.S.C. 120, 121 or 365(c). The Examiner calls to Applicants' attention the Examiner's inability to locate support for the following: 1) small interfering RNAs against polynucleotides encoding polypeptide SEQ ID NO:16; 2) to siRNA comprising claimed SEQ ID NO:13; and 3) the use of compositions comprising siRNA against polynucleotides encoding polypeptide SEQ ID NO:16 to treat any proliferative disease, such as cancer, within Application No. 60/414,867. As such, the Examiner assigns the current application an earliest effective filing date for claims 8, 10, 19, and 22, as July 29, 2003, the international filing date.

For purposes of expediting this examination, Applicants' acknowledge the earliest effective filing date of claims 8, 10, 19, and 22, with regard to the siRNA

embodiments, with SEQ ID NO:13, as July 29, 2003. Applicants reserve, however, rights under 37 C.F.R. 1.131 and related rules.

III. Claim Objections

The Examiner objected to claims 8, 19, 22, alleging that the claims recite non-elected subject matter. Specifically, the Examiner points out that the claims recite "antisense polynucleotides and non-elected targets (parts b and c of claims 8 and 19)."

In response, claims 8 and 19 have been amended, deleting parts (b) and (c) from both claims. Thus, the objection is obviated.

IV. Claim Rejections

A. 35 U.S.C. § 102(e)

Claims 8, 10, 19, and 22 were rejected under 35 U.S.C. § 102(e) for alleged anticipation by Arts *et. al.* (WO2004/094636). Applicants respectfully traverse the rejection in view of the present amendments.

To anticipate a pending claim, a prior art reference must provide, either expressly or inherently, each and every limitation of the pending claim. MPEP 2131. The Examiner contends that Arts *et. al.* discloses a siRNA *comprising* instant SEQ ID NO: 13 for the inhibition of the gene corresponding to Accession No. NM_022450 (corresponding to RHBDF1). However, the target sequence *consisting of* the nucleotide sequence of instant SEQ ID NO: 13 is not disclosed in Arts *et. al.*.

As amended, independent claims 8 and 19 now recite a siRNA to the nucleotide sequence consisting of SEQ ID NO: 13, as used in the working example of the specification.

Arts *et. al.* discloses a method for generating siRNA molecules. Applying their method to nucleotide databases, Arts *et. al.* identified nearly 12, 000 siRNA molecules, which they speculate, are capable of knocking down target gene expression. Of the nearly 12,000 siRNA molecules identified, only a handful were empirically tested.

In order to identify a functional siRNA, an examination to confirm the effectiveness of siRNA designed by a software program, to inhibit the expression of a target gene, is required. For example, Hanon *et. al.*, (Nature 431: 371-378 (2004)), cited by the Examiner, states that the discrimination between effective and ineffective siRNA molecules can only be accomplished by examining target protein level (page 373, Boxes 1, 2 "Several alleles are better than one," lines 6-8). Arts *et. al.* even point out that not every siRNA can effectively down regulate a gene (page 3, lines 17-20).

Although Arts *et. al.* discloses three target sequences of siRNA targeting RHBDF1 (SEQ ID NO: 8316, 8317, and 8318), no functional information of those sequences is provided.

Thus, siRNAs targeting RHBDF1 disclosed by Arts *et. al.* are required to be tested to confirm whether they inhibit the expression of RHBDF1. Such experimentation, if necessary, is undue for a person of skill in the art (MPEP 2164.01). Accordingly, Applicants insist that Arts *et. al.* does not meet the enablement requirement of 35 U.S.C. § 112, first paragraph.

The United States Supreme Court in *Seymour v. Osborn* held that a description in a prior art reference must contain a representation to enable any person skilled in the art to make, construct and practice the invention. 78 U.S. 11 Wall. 516 (1870); 78 U.S. 555, lines 1-8; Syllabus 18). Thus, Arts *et. al.*, because it does not meet

the enablement requirement, does not establish the prior art of the present application. Accordingly, Applicants believe that claims 8, 19 and 22 are novel over Arts *et. al.*.

Applicants submit that claims 8 and 19 and dependent claim 22, as amended, cannot be properly rejected for anticipation based on Arts *et. al.*. Therefore, the rejection should be withdrawn.

B. 35 U.S.C. § 103: Kawabata *et. al.*, Tuschl *et. al.* and Bass

Claims 8, 19, and 22 were rejected under 35 U.S.C. § 103(a) for alleged obviousness over Kawabata *et. al*. in view of Tuschl *et. al.* and Bass. The Examiner alleges that Kawabata *et. al.* discloses amino acid sequences corresponding to the peptide encoded by RHDBF1. While Tuschl *et. al.* and Bass purportedly represents a blueprint for the design and synthesis of siRNA molecules. Applicants respectfully traverse the rejection in view of the present amendment.

To support any rejection under 35 U.S.C. § 103 the examiner must provide a clearly articulated reason why the claimed invention would have been obvious. M.P.E.P. 2143. The Examiner, in the instant case, states that the "use of RNAi as a tool to determine gene function is *suggested* and *taught* by" Tuschl *et. al.* and Bass. Office Action, page 8. The Examiner concludes that "one of skill [in the art] would have been *motivated* and have had a *reasonable expectation of success*" to combine these teachings with those of Kawabata in "making and using siRNAs against polynucleotides encoding" SEQ ID NO:16. Id. Thus, the Examiner's articulated reasoning tracks one of seven recognized rationales that may support a finding of obviousness; namely, teaching, suggestion or motivation. M.P.E.P. 2143(G). Applicants respond accordingly.

To establish a prima facie showing of obviousness by the teaching, suggestion or motivation rationale, the Examiner must show that all the limitations of a

pending claim is expressly or impliedly taught by prior art references, there is a suggestion or motivation in the references for combining the limitations, and there exists a reasonable expectation of success in making the combination.

None of the references cited by the Examiner teaches or suggests the specific nucleotide sequence consisting of SEQ ID NO: 13 as a target sequence for siRNA suppression of RHBDF1 expression. The combination of these references does not supply all the elements of claims 8, 19, and 22. As such, Applicants submit that the obviousness rejection of claims 8, 19, and 22, based on the cited references, is improper and respectfully request its withdrawal.

C. 35 U.S.C. § 112, first paragraph

Claims 19 and 22 were rejected under 35 U.S.C. § 112, first paragraph, for alleged failure to comply with the enablement requirement. More specifically, the Examiner asserted that the terms "pharmaceutically effective amount and pharmaceutically effective carrier . . . requires that these claims be evaluated to determine whether the specification teaches how to use these compositions for treating any proliferative disease, particularly cancer." Applicants respectfully disagree and ask that the rejection be withdrawn.

It is well established that a specification is presumed to be in compliance with the enablement requirement of 112, first paragraph. The burden is on the Patent Office to establish a reasonable basis to question enablement. The test of enablement is whether one reasonably skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. For an examiner to sustain a rejection of the claims, in this case on the grounds of enablement, the examiner would have to provide evidence that the claimed nucleotides could not be made or used for any purpose, without undue experimentation.

In this case, Applicants wish to remind the Examiner that the pending claims are directed to *compositions of matter* (i.e., siRNA and pharmaceutical compositions) and not methods of using same. Accordingly, the Examiner's discussion of the unpredictability of siRNA administration and the hurdles associated with achieving *in vivo* therapeutic results are not relevant to the issue of enablement of the claimed compositions.

In fact, on the issue of "how to use," it is important to note that 112, first paragraph, does not require a specification to enable all uses of the claimed invention; rather, a single disclosed or well established use is all that is required. Furthermore, as noted in M.P.E.P. 2164.01(c), when a composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claimed is sufficient to preclude a rejection for non-enablement based on how to use. If multiple uses for claimed compositions are disclosed in the application, then an enablement rejection must include an explanation, sufficiently supported by the evidence, why the specification fails to enable each disclosed use. In other words, if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention.

In this instance, given the fact that Applicants have provided explicit working examples demonstrating utility and efficacy of the claimed embodiments to inhibit RHBDF1 expression and pancreatic cell growth *in vitro*, a rejection for lack of enablement is misplaced.

Implicit in the Examiner's enablement challenge is the suggestion that certain compositions within the scope of the instant claims (*e.g.*, certain siRNA sequences) may not, in fact, prove to be therapeutically efficacious. However, the fact that a generic claim might encompass some possibly inoperative embodiments is not enough in itself to render the claim unpatentable. *Atlas Powder v. E. I. Dupont de*

Nemours, 750 F.2d 1569, 1576 (Fed. Cir. 1984). In any event, such potentially inoperable embodiments are excluded from the claims as the pending claims expressly or inherently require that the siRNA molecule be capable of inhibiting expression of RHBDF1.

As for the Examiner's specific grounds for challenging the enablement of siRNA therapy, Applicants submit that the allegations presented herein would seemingly apply to any claim that encompasses nucleotide-based compositions and therapies. Accordingly, it appears that the Examiner finds the entire field of "gene therapy" to be fundamentally and irredeemably unpredictable. In fact, from the context of the instant rejection, one would presume that an applicant could never obtain protection for a claim that encompasses *in vivo* gene therapy without both conclusive human clinical trial data and extensive detail regarding administration parameters. Even then one would be restricted to the specifics of the embodiments actually tested (*i.e.*, specific vector, administration route, disease, etc.).

This is clearly both unreasonable and in conflict with statute, and rules and guidelines of the M.P.E.P.. For example, M.P.E.P. 2107.01 and 2107.03 clearly state that an applicant need not demonstrate that the invention is completely safe. Furthermore, under case law, Applicants need not prove clinical efficacy to show that a therapeutic process is operable (*i.e.*, enabled). As stated in M.P.E.P. 2107.01, the "courts have found utility for therapeutic inventions, despite the fact that an applicant is at a very early stage in the development of a therapeutic regimen" or that a therapeutic treatment regimen is not at a stage where it is ready to be practiced on humans. *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985); *In re Brana*, 51 F.3d 1560, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Moreover, it is not within the province of the USPTO to require proof of efficacy in animals prior to granting a patent that encompasses therapeutic methods.

In fact, the PTO guidelines are explicit on this point:

> "Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trails. There is no decisional law that requires an applicant to provide data from human clinical trials to establish utility [i.e., operability and enablement] for an invention related to treatment of human disorders." M.P.E.P. 2107.03.

The guidelines further state that "[t]he Office must confine its review of patent applications to the statutory requirements of the patent law, and in quoting *In re Brana*, *supra*, that "FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of patent laws."

Thus, the Examiner's requirement for *in vivo* working examples seems to be in clear conflict with statutory and case law. Furthermore, it is well settled that the patent laws merely require that a "reasonable correlation" exist between the scope of the claims and the scope of enablement. In other words, if the art is such that a particular assay or model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one of skill in the art would accept the model as reasonably correlating with the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995). Since the initial burden is on the Examiner to give reasons for lack of enablement, the Examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. Importantly, a rigorous or an invariable exact correlation is not required. *See Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739, 747 (Fed. Cir. 1985).

In the instant case, the Examiner cites to a generic "lack of guidance" and "unpredictability in the art" to support the Examiner's summary conclusion that the present claimed invention is not enabled, dismissing Applicants conclusive

demonstration that transfection of chronic myeloid leukemia or lung cancer cells with siRNA directed against endogenously expressed RHBDF1, a gene shown to be highly over-expressed in a majority of chronic myeloid leukemia patient samples, results not only in a reduction of endogenous RHBDF1 expression but further results in "drastic growth suppression," as measured by both the colony formation assay and the MTT assay. Furhter, an accumulation of a chronic myeloid leukemia cancer is found in blood (http://en.wikipedia.org/wiki/Chronic_myelogenous_leukemia), so the administration of a siRNA targeting for a chronic myeloid leukemia cancer cell expressing RHBDF1 would be effective to chronic myeloid leukemia cancer.

Given that positive *in vitro* findings are routinely correlated to positive *in vivo* findings, the burden is on the Examiner to demonstrate that one skilled in the art would not reasonably extrapolate the undisputed positive results to treatment in a mammal, a burden the Applicants respectfully submit the Examiner has not met. Accordingly, Applicants respectfully submit that a reasonable correlation exists between the scope of the claims and the scope of enablement and the working examples.

The proper standard for compliance with enablement is not absolute predictability but objective enablement. In that vein, supporting evidence need not be conclusive but merely convincing. The Applicants respectfully submit that the compelling data presented in the instant specification is sufficiently convincing that one of ordinary skill in the art would not doubt the feasibility of the claimed invention or its application to living systems, including humans.

Notwithstanding the ample evidence supporting the enablement of the present invention, the Examiner nevertheless asserts that significant obstacles are associated with siRNA therapy, including, for example, "delivery, distribution and clearance" of the siRNA molecule. However, the fact that certain hurdles may exist in the art in terms of improving efficacy and efficiency of human clinical therapy does not

undermine the fact that Applicants have conclusively demonstrated that the invention as claimed is suggestive of a therapeutically beneficial result.

Moreover, the Examiner's speculative concerns are moot in light of the experimental evidence presented herein. As the instant examples amply demonstrate, administration of siRNA against RHBDF1 has a significant effect on growth and survival of chronic myeloid leukemia or lung cancer cells. While this perhaps does not rise to a "cure" for chronic myeloid leukemia or lung cancer and while booster administration may ultimately be necessary to achieve long term benefits, the results nevertheless support the enablement of "treatment," i.e., a procedure or application intended to relieve, ameliorate or assuage illness or injury. It is well established that even transient expression can confer some therapeutic benefit. The fact that a noted therapeutic effect may disappear over time does not undermine the utility and operability of the invention as claimed.

Thus, the Examiner's demand for proof of stable or long term gene expression is misplaced. Accordingly, Applicants respectfully submit that the objective findings of the instant examples clearly support enablement of the claimed invention and outweigh the generic speculations of the prior art and that the long term efficacy is not required to demonstrate enablement of the present invention.

On the issue of direction or guidance provided, Applicants' specification not only describes administration protocols (page 33, lines 6-25), but also provides a detailed protocol for selecting siRNA target sites and designing siRNA molecules (page 24, lines 24-31) suitable for use in the context of the claimed invention. Not only has the Examiner completely ignored this disclosure, but has failed to provide any reasons for doubting the truth and accuracy of these statements. Instead, the Examiner focuses on the issue of "tissue targeting" and the alleged difficulties associated therewith.

In support of this conclusion, the Examiner cites to Hanon *et. al.*, for the premise that delivery, distribution, degradation and clearance constitute "important issues and concerns about the therapeutic application of this technology, including difficulties with delivery and uncertainty about potential toxicity." Nature, 431: 371-378 (2004). However, this appears to be in conflict with the disclosure of Hanon *et. al.* on page 374, 2nd column, lines 17-19 which states that "proposals for clinical trails using either synthetic siRNAs or viral vector derived shRNAs have been put forward" and pages 375, 2nd column, lines 12-17 which states that "[i]n a continuing clinical trial, T lymphocytes from a HIV infected individuals are transduced *ex vivo* with a lentiviral vector that encodes an anti-HIV antisense RNA. . . . This type of therapeutic approach would be applicable to vectors harboring genes that encode siRNAs."

The *in vitro* successes documented in the Examples of the instant specification clearly outweigh any speculative allegations of unpredictability. The Applicants respectfully submit that one reasonably skilled in the art, given the explicit disclosure in the specification of specific *in vitro* working examples, using models that reasonably correlate to *in vivo* therapy, would be able to make and use the invention without undue experimentation.

Thus, for the forgoing reasons, Applicants respectfully submit that the scope of the pending claims are commensurate with the instant specification's scope of enablement. Accordingly, the Applicants respectfully request that the Examiner reconsider and withdraw the enablement rejection in view of the amendments to the claims and the remarks therein.

CONCLUSION

In view of the foregoing, Applicants NAKAMURA and KATAGIRI believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at .

Respectfully submitted,

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